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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	09/899,440	STEIN, CY	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1--28* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 & 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Objections

Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 is drawn to the oligo of claim 1 that comprises a modified internucleoside linkage. However, the oligo of claim 1 already possesses a phosphorothioate linkage, which is a modified internucleoside linkage. Thus, claim 8 is restating a limitation that already exists in claim 1. Claim 9 ostensibly limits claim 8 to one of four types of modified internucleoside linkages; however, one of the listed species is a phosphodiester linkage, which is the native linkage of oligonucleotides, and thus not a modification as stipulated in claim 8. Claim 9 effectively removes a limitation of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claim recites "the oligonucleotide of claim 1, wherein the sequence of the oligonucleotide is selected from the following:" and then lists three sequences that are separated by the conjunction "and". Such use of the term "and" leaves the claims unclear as to whether one, two or all three will be selected. If only one is intended to be selected, the sequences should be separated by the term "or". If applicant intends otherwise, clarification is required to reflect the scope of the claim.

Claim 20 contains the trademark/trade name LIPOFECTIN. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a cationic nucleotide carrier and, accordingly, the identification/description is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8 and 10-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claim 1 of the above inventions is drawn to any "oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase".

The specification provides a description of a heparanase polynucleotide isoform that comprises the target, represented by SEQ ID NO. 17. However, the specification goes on to

define all references to heparanase as encompassing all heparanase variants, natural or otherwise, that may be within 80% similarity of said heparanase, wherein said similarity may include conservative nucleotide substitutions so long as heparanase function is retained. Additionally, the language of claim 1 broadly contemplates sequences complementary to *any* heparanase. The specification as filed does not appear to disclose any additional species of heparanase other than that disclosed at SEQ ID NO. 17. Since the language of claim 1 clearly encompasses all antisense oligonucleotides that may be complementary to a heparanase, the person of ordinary skill in the art would need to be able to determine from the present specification a representative number of polynucleotide sequences of heparanase that might comprise such targets, in order to determine the suitable complements of each heparanase sequence and thus practice the invention as claimed.

In order to envision the genus of such heparanase targets, the specification should include a representative sample from heparanases of all species that express said protein, all isoforms and alleles present within each of these species, and finally all variants that are within 80% similarity of said protein that retain heparanase function. A person of skill in the art would not view SEQ ID NO 17 of the specification as being representative of the broad genus of all heparanases claimed, and would thus conclude that applicant was not in possession of the invention as broadly contemplated. Moreover, without a specific description of additional sequences or specific domains or motifs having the requisite heparanase activity, the skilled artisan would not readily envision any other target beyond SEQ ID NO17. The specification thus

provides description for SEQ ID NO 17, but not for sequences that are antisense to any polynucleotide encoding heparanase that are heretofore undescribed.

Claims 15, 16, and 21-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of heparanase expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of heparanase expression *in vivo* (whole animals) or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of heparanase in a cell which may be a cancer cell comprising contacting said cell with antisense compositions that inhibit the expression of heparanase. The claims of the above invention are also drawn to methods of treating a subject having a condition associated with heparanase, wherein said compositions are administered to animals such that expression of heparanase is inhibited, wherein said condition may be cancer, which may be characterized by tumor metastasis, or involves reduction of angiogenesis, wherein the language of said claims encompasses *in vivo*

activity. The specification teaches a method of using the claimed compositions to inhibit the expression of heparanase in T24 bladder carcinoma cell line.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2).

Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to

generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of heparanase expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with heparanase expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to compounds and methods of treating or preventing any condition or disease suspected of being associated with heparanase expression in humans. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring heparanase expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo,* and further, that treatment and/or preventive effects

are provided for any and/or all diseases or conditions suspected of being associated with heparanase expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with heparanase expression in humans, or their tissues or cells, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-6, 8-12, 14, 17-19 and 28 rejected under 35 U.S.C. 102(b) as being anticipated by Graham et al., WO 96/08559.

The claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is 10-40 nucleotides long, contains at least one phosphorothioate linkage, inhibits at least 50% as measured by western blot, wherein said oligo is made of DNA or RNA, or wherein said oligo is composed of 100% phosphorothioate linkages, or wherein said oligo is 15-25 nucleotides long, or is 20 nucleotides long, or comprises a internucleoside, sugar, or base modifications, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase.

Graham et al. teach oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase, wherein said oligo is 10-40 nucleotides long, contains at least one phosphorothioate linkage, and fully inhibits expression, wherein said oligo is made of DNA or RNA, or wherein said oligo is composed of 100% phosphorothioate linkages, wherein said oligo is about 20 nucleotides and comprises internucleoside, sugar, and base modifications, wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase. Applicant's inclusion of a western blot protocol as the assay of choice to verify inhibition of heparanase expression in claim 1 is a design choice that doesn't influence the patentability of the oligonucleotide itself, and has not been treated as materially important in the present examination.

Claim 1-3, 5, 6, 14, 17-19, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Pecker et al. (WO 00/52178).

The claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 to 40 nucleotides long, may contain at least one phosphorothioate linkage, inhibits heparanase expression at least 50% as measure by western blot, wherein said oligo is made of DNA or RNA, or is made of 15-25, or about 20 nucleotides, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide can be used for the formation of pharmaceutical compounds, or inhibits expression of human heparanase.

The claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 nucleotides long, may contain at least one phosphorothioate linkage, inhibits heparanase expression, wherein said oligo is made of DNA or RNA, or may comprise internucleoside, sugar, or base modifications, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graham et al., in view of Froehler et al. (U. S. Patent No. 5,484,908).

Claim 13 of the instant application is directed to the antisense oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 to 40 nucleotides long, contains at least one phosphorothioate linkage, wherein said oligo inhibits heparanase expression, wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine.

Graham et al. teaches antisense oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 to 40 nucleotides long, contains at least one phosphorothioate linkage, wherein said oligo inhibits heparanase expression, and teaches nucleobases modifications to said oligo, but does not teach 5-methyl pyrimidine or 5-propynyl pyrimidine modifications.

Froehler et al. teaches 5-propynyl pyrimidine modifications of oligo nucleobases.

It would have been obvious for one of ordinary skill in the art to take the heparanase antisense oligos as taught by Graham et al. and incorporate 5-propynyl pyrimidine modifications into them as taught by Froehler et al. One would have been motivated to do so because Froehler et al. teach that such modifications enhance binding of the antisense oligo to the target gene, which is the key step in antisense oligo-mediated inhibition. One of ordinary skill in the art would have had a reasonable expectation of success in doing so, because Froehler et al. provide detailed instructions on its synthesis, and because such modifications are routinely performed by those of ordinary skill in the art. Thus, in the absence of evidence to the contrary, the invention of claim 13 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
August 21, 2002

ANDREW WANG
PRIMARY EXAMINER